PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

(Attorney No. SIR-MIS-00001-US-CIP[2])

IN THE APPLICATION OF:		)		
		)		
McSwiggen *et al.*		)		
		)		
Serial No.	**10/693,059**	)	**Examiner:**	**Pitrak**
		)		
Filed:	**October 23, 2003**	)	**Group Art Unit:**	**1635**
		)		
Title	**RNA Interference Mediated Inhibition of Gene Expression Using Chemically Modified Short Interfering Nucleic Acid (siNA)**	)	**Confirmation No.:**	**1557**

BRIEF ON APPEAL

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BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This is an appeal from the Final Rejection mailed February 3, 2009 and Advisory Action mailed June 15, 2009. This brief is submitted along with the small entity fee of $255. A notice of appeal was filed on June 23, 2009. Also submitted herewith is a petition for a two (2)-month extension of time, and the appropriate fees in connection with that petition. In the event of any variance between the amounts enclosed and the Patent and Trademark Office charges, the Commissioner is authorized to charge or credit any difference to our Deposit Account No. 50-4615.

Contents

REAL PARTY IN INTEREST

The real party in interest is Sirna Therapeutics, Inc., which is a wholly owned subsidiary of Merck & Co. Inc..

RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending.

STATUS OF CLAIMS

Claims 18 and 20-33 are pending and stand rejected. Claim 18 has been amended. A copy of the claims on appeal is attached in Appendix A. A copy of the amended claim is attached in Appendix D.

STATUS OF AMENDMENTS

A Final Office Action was mailed on February 3, 2009. A first response to Final Office Action was filed on May 28, 2009, wherein claim 18 was amended to more exactly state the first strand as the sense strand and the second strand as the antisense strand. An Advisory Action was mailed on June 15, 2009. Claim 18 has been amended in part c) to recite "the sense strand, antisense strand, or both strands comprise five or more nucleotides each having a Northern conformation modification; …." No other amendments have been made.

SUMMARY OF THE CLAIMED SUBJECT MATTER

The invention provides certain chemically modified double stranded nucleic acid molecules, each comprising a sense strand and a separate antisense strand of 19 to 29 nucleotides in length, wherein the sense strand, the antisense strand, or both the sense and the antisense strands comprises five or more nucleotides that are each modified by a Northern conformation modification, and at least two of the Northern modifications are different from each other. *See* claim 18; Specification at, *inter alia,* page 8, lines 24-27; page 11, lines 22-24; page 40, line 22, to page 41, line 27; page 41, line 28, to page 42, line 2; Figures 18, 19; Tables I & IV.

Each of the molecules above can comprise one or more ribonucleotides, and thus are not fully or completely chemically modified. *See* claim 20; Specification at, *inter*

alia, page 44, line 27, to page 45, line 21; page 79, lines 5-6, Figures 18 and 19, Tables I & IV.

The Northern conformations that are present in the molecules above can be those selected from the group consisting of locked nucleic acid (LNA); 2'-methoxyethyoxy; 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro, 2'-deoxy-2'-chloro, 2'-azido, 2'-O-trifluoromethyl, 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro, 2'-deoxy-2'-chloro, 2'-azido, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, 4'-thio and 2'-O-methyl modifications. *See* claim 21; Specification at, *inter alia,* page 42, lines 2-6.

Each of the molecules above can include a terminal cap moiety at the 5'- end, the 3'-end, or both of the 5' and 3' ends of the sense strand. *See* claim 22; Specification at, *inter alia,* page 12, lines 12-14; page 21, lines 5-7; page 36, lines 20-23; Figures 18 & 19;

Each of the molecules above can include a terminal cap moiety at the 3'-end of the antisense strand. *See* claim 23; Specification at, *inter alia,* page 39, lines 22-25; page 45, line 22, to page 46, line 27; page 50, lines 5-32; page 71, lines 26-30.

The terminal cap moieties of the molecules above can comprise an abasic moiety, and the deoxy abasic moieties can further be an inverted deoxyabasic moiety. *See* claims 24-27; Specification at, *inter alia,* page 12, lines 15-16; page 17, lines 14-17; page 21, lines 7-8; page 72, line 21, to page 73, line 6.

Any of the pyrimidine nucleotides in the sense strand of each of the modified double stranded nucleic acid molecule may be a 2'-O-methyl pyrimidine nucleotide. *See* claim 28; Specification at, *inter alia,* page 11, lines 27-30; page 20, lines 28-31; Figure 18C, Table I & IV (*e.g.,* stab 6).

Any of the purine nucleotides in the sense strand of each of the modified double stranded nucleic acid molecule may be a 2'-deoxy purine nucleotide. *See* claim 29; Specification at, *inter alia,* page 11, line 27, to page 12, line 3; page 17, lines 9-12; page 20, lines 28-31; page 21, lines 1-4; page 36, line 24, to page 37, line 3; Figures 18 & 19, Tables I & IV.

Any of the pyrimidine nucleotides in the sense strand of each of the modified double stranded nucleic acid molecule may also be 2'-deoxy-2'-flouro pyrimidine nucleotides. *See* claim 30; Specification at, *inter alia,* page 11, line 30, to page 12, line 3;

page 17, lines 9-14; page 21, lines 1-4; page 37, lines 4-14; Figures 18 & 19; Tables I & IV.

Any of the pyrimidine nucleotides in the antisense strand of each of the modified double stranded nucleic acid molecule may also be a 2'-deoxy-2'-fluoro pyrimidine nucleotide. *See* claim 31; Specification at, *inter alia,* page 12, lines 4-11; page 17, lines 17-19; page 21, lines 9-12; page 29, lines 9-15; page 38, lines 5-25; Figures 18 & 19, Tables I & IV.

Any of the purine nucleotides in the antisense strand of each of the modified double stranded nucleic acid molecule may be a 2'-O-methyl purine nucleotide. *See* claim 32; Specification at, *inter alia,* page 12, lines 4-7; page 15, lines 15-16; page 17, lines 17-19; page 21, lines 9-12; page 37, line 15, to page 38, line 4; Figures 18 & 19, Tables I & IV.

The present invention also pertains to a composition comprising one of the molecules depicted above in a pharmaceutically acceptable carrier or diluent, or a cell comprising such a molecule. *See* claim 33; Specification at, *inter alia,* page 62, lines 16-21.

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The only issue on appeal is whether claims 18 and 20-33 are obvious under 35 U.S.C. § 103(a) over Elbashir *et al.* (2001, EMBO J., v. 20(23): 6877-88), Monia & Cowsert (U.S. Patent 6,033,910), Matulic-Adamic *et al.* (U.S. 5,998,203), and Pieken *et al.* (Science, 253:314-317 (1991)).

ARGUMENT

Claims 18 and 20-33 are not *prima facie* obvious in view of the cited references, and are allowable. At the outset, the Office misconstrued the instant claims and premised its obviousness finding on that misconstruction. The Office also fails to note that the cited references alone or in combination do not teach the claim limitation of an RNAi activity-compatible chemical modification pattern containing at least ***two different modifications in a single molecule***. This missing limitation was not fairly suggested or taught by the cited references or the general knowledge in the prior art, because there was no way of predicting with any confidence which and how known stabilizing modifications might be detrimental the RNAi activity of a short nucleic acid duplex. Accordingly, Applicants respectfully request that the Office's finding of obviousness be overturned.

I. The Office misconstrues the instant claims

Applicants respectfully submit that the Office has misconstrued the instant claims by neglecting an important limitation in instant claim 18. In the Final Office Action and the Advisory Action, the Office repeatedly asserted that claimed molecules are similar to those taught by the references because the asserted references indicated that different modifications could be applied to siRNA molecules. *See, e.g.,* Advisory Action, at page 2, paragraph 2 ("both 2'-deoxy and 2'-O-methyl-modified nucleotides can effectively be used at the ends of siRNAs, as shown for 2'-deoxy in Figure 4, but not throughout the siRNA."); at page 2, paragraph 3 ("the Monia reference teaches that modified olig[o]nucleotides of their invention may contain ONE OR MORE substituted sugar moieties, preferably those listed in column 8, which include 2'-OMe and 2'-MOE (2'-methoxyethoxy) modifications.").

Contrary to the Office's contentions, however, none of the cited references taught or suggested a single molecule that is modified with two different types of modification in a single molecule. The number of nucleotides that are modified in a given molecule is an entirely different concept from the types of modified nucleotides in that molecule, but the Office appeared to have read them indiscriminately or interchangeably. Properly

read, the instant claims 18 and 20-23 recites ***both*** at least five modified nucleotides in one or both strands, ***and*** at least two types of modifications.

II. The cited references in combination do not teach or suggest a single siRNA duplex modified with at least two different types of modifications.

The references cited by the Office, alone or in combination, do not teach or suggest each and every claim limitation of claims 18 and 20-33, especially the limitation requiring that "at least two of said modifications are different from each other." As such, the instant claims are not *prima facie* obvious and the claims are allowable.

The Supreme Court's decision in *KSR International Co. v. Teleflex Inc.,* 127 S. Ct. 1727 (2007) does not change the first step in an obviousness determination as previously promulgated by the Federal Circuit Court of Appeals (CAFC): ***ascertaining that each and every claim limitation has been disclosed or suggested by the prior art.*** This first step was again affirmed by the CAFC in a recent decision, *Abbott Laboratories v. Sandoz,* 2007-1300, *16 (Fed. Cir. October 21, 2008), where the district court's interpretation of the *KSR* opinion in this respect was said to be correct:

> *The KSR opinion only focused on the Federal Circuit's strict use of the TSM [teaching, suggestion, motivation] test in performing the obviousness analysis; it did not mention or affect the requirement that* ***each and every claim limitation must be found present*** *in the combination of the prior art references before the analysis proceeds.*

Id. at *16-*17 (*emphasis added*). Therefore, unless the cited references taught or suggested the every claim limitation, the claims are not obvious.

Here, the only reference relating to siRNAs is Elbashir. However, Elbashir taught incorporating 2'-deoxy nucleotides in one or both strands, ***or*** incorporating 2'-O-methyl nucleotides in one or both strands, but ***not both.*** As such, Elbashir did not teach or suggest a single siRNA molecule having ***at least two different modifications.***

The deficiency of Elbashir cannot be remedied by the disclosures of the Monia, Piekin or Matulic-Adamic, taken together, because modifications that were commonly known to ***stabilize*** antisense molecules (Monia) against nuclease degradation have been reported to be ***detrimental to RNAi activity*** if applied to an siRNA molecule beyond the terminal nucleotides or if at all, as evidenced by the Elbashir reference cited herein.

Indeed, Elbashir reported, in no uncertain terms, that 2'-deoxy modification, one of the most commonly used chemical modifications on antisense molecules (*e.g.,* as reported in the Monia reference herein), must be limited to the 3'-terminal overhanging nucleotides and/or the two nucleotides immediately adjacent thereto, and extensive 2'-deoxy modification on an siRNA molecule abrogates activity. Another commonly used chemical modification, 2'-O-methyl (also reported in the Monia reference herein), should not be used at all. *See* Elbashir, at page 6885, left column, lines 7-13:

> ***2'-deoxy substitution of the 2 nt 3'-overhanging ribonucleotides*** *do not affect RNAi, but help to reduce the costs of RNA synthesis and may enhance RNAse resistance of siRNA duplexes.* ***More extensive 2'-deoxy or 2'-O-methyl modifications reduce the ability of siRNA to mediate RNAi,*** *probably by interfering with protein association for siRNP assembly.*

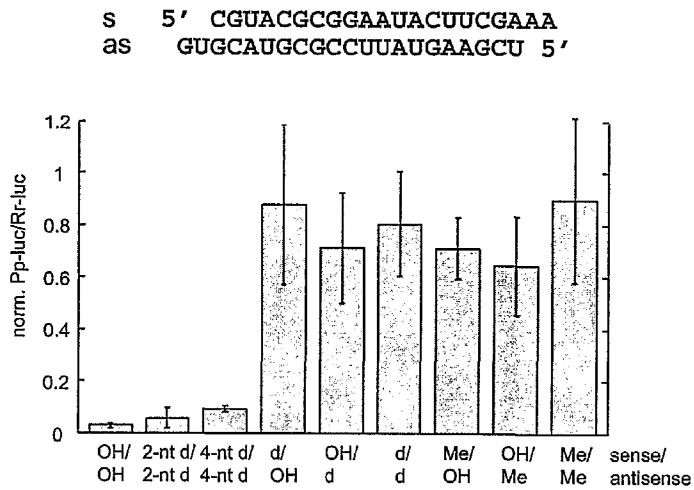
(*emphasis added*).

On the other hand, the Office repeatedly argued that "Elbashir teaches that siRNAs with 2'-deoxy nucleotides at the end of siRNA strands were functional and ***suggested that siRNAs with 2'-OMe nucleotides at the end of siRNA strands were also functional,***" (Final Office Action, at page 3; Advisory Action, at page 2). But after an exhaustive search of the Elbashir reference, no suggestion can be found to indicate that the terminally 2'-OMe-modified siRNA were functional. The figure and paragraphs cited by the Office reported siRNA functionality ***only*** when 2'-deoxy modification was applied at the 3'-ends. In fact, every mention of 2'-OMe modification was tied to a ***lack of functionality***.

For ease of comparison, Applicants quote the Elbashir passage in the last paragraph of page 6881:

> *To assess the importance of the siRNA ribose residue for RNAi, duplexes with 21-nt siRNAs and 2-nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleoties had no effect and even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region produced significantly active siRNA. Thus, 8 out of 42 nt of a siRNA duplex were replaced by DNA residues without loss of activity. Complete substitution of one or both siRNA strands by 2'-deoxy residues, however, abolished RNAi, as did complete substitution by 2'-O-methyl residues.*

Figure 4 is also reproduced here, and the constructs of this figure are separately aligned with the description of this figure in the above-quoted paragraph from page 6881:



Sense/antisense	Description in last paragraph, p. 6881	RNAi function, last paragraph, p. 6881
OH/OH	Native, unmodified, or all-RNA duplex	
2-nt d/2-nt d	"[s]ubstitution of the 2nt 3'-overhangs by 2'-deoxynucleotides"	"had no effect"
4-nt d/4-nt d	"even the replacement of two additional ribonucleotides by 2'-deoxyribonucleotides adjacent to the overhangs in the paired region"	"produced significantly active siRNA"
d/OH	"[c]omplete substitution of one … siRNA strand[] by 2'-deoxy residues"	"abolished RNAi"
OH/d	"[c]omplete substitution of one … siRNA strand[] by 2'-deoxy residues"	"abolished RNAi"
d/d	"[c]omplete substitution of … both siRNA strands by 2'-deoxy residues"	"abolished RNAi"
Me/OH	"complete substitution by ***2'-O-methyl*** residues"	"***abolished*** RNAi, as did complete substitution by ***2'-O-methyl*** residues"
OH/***Me***	"complete substitution by ***2'-O-methyl*** residues"	"***abolished*** RNAi, as did complete substitution by ***2'-O-methyl*** residues"
Me/Me	"complete substitution by ***2'-O-methyl*** residues"	"***abolished*** RNAi, as did complete substitution by ***2'-O-methyl*** residues"

(emphasis added, to descriptions related to 2'-O-methyl modification).

As such, Elbashir clearly teaches that 2'-deoxy or 2'-O-methyl modifications, which were ***known to protect antisense molecules against nuclease degradation*** are in fact ***not desirable*** in the siRNA context because they largely cause loss of RNAi activity. If these commonly ***known stabilizing modifications*** are ***detrimental to RNAi activity***, then there is no reasonable expectation that other known chemical modifications, such as the 2'-F modification of Monia/Pieken and terminal cap moieties of Matulic-Adamic, and

other known motifs, such as the gampers of Monia, could be applied to siRNA molecules without abrogation of RNAi activity, even if those modifications could indeed improve nuclease resistance. Nor was there an expectation that the gapmer motifs of Monia, which allegedly were beneficial to "enhance stability" of antisense molecules (Advisory Action, at page 2), would be suitable for an siRNA molecule. There was simply no correlation in the art tying nuclease stability to RNAi activity.

The Court of Appeals at the Federal Circuit recently held in *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.,* 567 F.3d 1314 (Fed. Cir. 2009) that a prior art reference teaches away from the claimed invention if a combination would not have worked for the intended purpose of the claimed invention, specifically where "the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements." 567 F. 3d. at, 1325-28. In this case, from the teachings of Elbashir, those skilled in the art would know to refrain from modifying with any known stabilizing modifications other than 2'-deoxy, and to avoid modifying beyond 4 nucleotides at the 3'-terminal ends. Thus Elbashir clearly teaches away from combining with the other cited references, all of which describe nothing more than known stabilizing modifications.

The Office appears to rely on Monia as suggesting the application of two or more different types of modifications in a single molecule, asserting that "Monia teaches the use of ***two different modifications*** at the ends of antisense oligonucleotides to increase oligonucleotide stability," (Final Office Action, at page 3), but the Office provided no basis for such an assertion. As explained above, known modification motifs in the antisense and ribozyme areas cannot be predictably applied to siRNAs. But even assuming, *arguendo,* that they can be so applied, Monia still does not teach a single molecule having two or more types of Northern conformation modifications.

It should be noted that antisense molecules of Monia inhibit gene expression by an RNase H mechanism, wherein the enzyme RNase H recognizes and cleaves the mRNA target in an RNA:DNA duplex. Thus, an antisense gapmer molecule in its native and unmodified form has at least a DNA region that would form a duplex with the mRNA target, which allows for the recruiting of RNase H and knockdown of gene expression. In a chimeric or "gapmer" construct, such as the ones described in Monia,

the ends of the antisense strand, or the "wings" can be modified to enhance stability. Among the gapmers in Monia, however, ***none*** can be found to use ***two different modifications*** in the wings of a single molecule. *See, e.g.,* Example 5 ([2'-O-Me]-[2'-deoxy]-[2'-O-Me] chmieric phosphorothioate oligonucleotides (col. 34, line 24, *et seq*); [2'O-(2-methoxyethyl)]-[2'-deoxy]-[2'-O-(2-methoxyethyl)] chemiric phosphorothiate oligonucleotides (col. 34, line 50, *et seq*); [2'-O-(2-Methoxyethyl)Phosphodiester]-[2'-deoxy-phosphorothiate]-[2'O-methoxyethyl)phosphodiester] chimeric oligonucleotides (col. 34, line 57, *et seq*); Example 16 (2'-MOE gapmers, wherein the wings are 2'-methoxyethyle nucleotides). Thus, the Office's statement that Monia "teaches that modified olig[o]nucleotides of their invention may contain ONE OR MORE substituted sugar moieties, preferably those listed in column 8, which include 2'-OMe and 2'-MOE modifications" (Advisory Action, at page 2) is misleading at best because the Monia gapmers either have 2'-OMe wings ***or*** 2'-MOE wings, but ***not both.*** Therefore, each of the Monia gapmers has a single type of Northern conformation modification. Moreover, even assuming, *arguendo,* that an RNA-based antisense molecule was contemplated in the art, the Monia gapmers would still have only a single type of Northern conformation modification per molecule because a 2'-deoxy modification of RNA does not have a Northern conformation.

Furthermore, the Office's arguments of obviousness hinges on the notion that those skilled in the art would have been motivated to try known modifications that had been used to enhance nuclease stability in the antisense and ribozyme arts in an siRNA context. But this reasoning does not square with the fact that each of the antisense and ribozyme references cited by the Office disclosed a very large number of modifications that were known to stabilize nucleotides against nucleases, but none provided direction as to which of these to apply in the siRNA context so as to preserve RNAi functionality. It is important to note that the issue has never been whether the modifications selected by the instant Applicants would enhance nuclease stability, but rather whether there was anything in the art to teach or suggest with specificity which of those known stability-enhancing modifications could be applied to an siRNA without abrogating RNAi functionality.

It is respectfully submitted that the number of known stability-enhancing chemical modifications is huge. For example, Monia describes, in the antisense context, that oligonucleotides can be modified in the backbones or into non-naturally occurring portions "because of desirable properties such as, for example, enhanced cellular uptake, enhanced affinity for nucleic acid target, and increased stability in the presence of nucleases." Col., lines 21-24. Preferred modified oligonucleotides backbones include, for example:

> *phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotriesters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, and boranophosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein the adjacent pairs of nucleoside units are linked 3'-5' to 5'-3' or 2'-5' to 5'-2'. Various salts, mixed salts and free acid forms are also included.*

See, paragraph bridging columns 6-7. Moreover, preferred modified oligonucleotide backbones that do not include a phosphorus atom may be:

> *backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and* CH_2 *component parts.*

See, column 7, lines 22-37. Furthermore, in other preferred oligonucleotide mimetics, both the sugar and the backbone can be replaced with novel groups, such as a PNA. *See,* column 7, lines 48-55. And most preferred embodiments are oligonucleotides with phosphorothioate backbones and oligonucleosides with heteroatom backbones:

> *and in particular* $-CH_2-NH-O-CH_2-$, $-CH_2-N(CH_3)-O-CH_2-$ *[known as a methylene (methylimino) or MMI backbone],* $-CH_2-O-N(CH_3)-CH_2-$, $-CH_2-N(CH_3)-N(CH_3)-CH_2-$ *and* $-O-N(CH_3)-CH_2-CH_2-$ *[wherein the native phosphodiester backbone is represented as* $-O-P-O-CH_2-$*] of the above referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above referenced U.S. Pat. No. 5,602,240. Also preferred are oligonucleotides having morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.*

See, paragraph bridging columns 7-8. As to sugar modifications, Monia states that "[p]referred oligonucleotides comprise one of the following at the 2'-position:"

> *OH; F; O-, S-, or N-alkyl; O-, S-, or N-alkenyl; O-, S- or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C_1 to C_{10} alkyl or C_2 to C_{10} alkenyl and alkynyl. Particularly preferred are $O[(CH_2)_n O]_m CH_3$, $O(CH_2)_n OCH_3$, $O(CH_2)_nNH_2$, $O(CH_2)_nCH_3$, $O(CH_2)_nONH_2$, and $O(CH_2)_n ON[(CH_2)_n CH_3)]_2$, where n and m are from 1 to about 10.*

See, column 8, lines 11-21. Other preferred oligonucleotides may comprise one of the following at the 2' position:

> *C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH_3, OCN, Cl, Br, CN, CF_3, OCF_3, $SOCH_3$, $SO_2 CH_3$, ONO_2, NO_2, N_3, NH_2, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O-$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., Helv. Chim. Acta, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-dimethylaminooxyethoxy, i.e., a $O(CH_2)_2 ON(CH_3)_2$ group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH_2-O-CH_2-$N(CH_2)_2$, also described in examples hereinbelow.*

See, column 8, lines 22-42. Monia does not stop there, but went on to list even more preferred modifications:

> *include 2'-methoxy (2'-O-CH_3), 2'-aminopropoxy (2'-$OCH_2CH_2CH_2NH_2$) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar. Representative United States patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos. 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; and 5,700,920, certain of which are commonly owned with the instant application, and each of which is herein incorporated by reference in its entirety.*

See, column 8, lines 43-59. In addition, Monia lists modified nucleobases other than those above, which are said to be "particularly useful for increasing the binding affinity of the oligomeric compounds." *See, e.g.,* paragraph bridging columns 8-9.

It is therefore clear that, if a skilled person in the art were to test all stability-enhancing modifications known in the antisense art ***alone,*** he would have at least all of the ones listed in the quotes above to select from. That is by no means a small number, but ***it gets larger still*** if the skilled person also considers modifications suitable for use in the ribozyme art. For example, the cited Matulic-Adamic reference taught that "modifications protect the enzymatic nucleic acids from exonuclease degradation, … facilitates efficient uptake … by cells, … and help achieve an overall improvement in the efficacy of ribozymes in vitro and in vivo." *See,* Matulic-Adamic, at col. 2, lines 44-58. Matulic-Adamic went on to list the suitable modifications as including, but not limited to: (1) terminal modifications (*i.e.,* either a 5'-cap or a 3'-cap); (col. 2, lines 47-49); (2) modified bases (col. 4, line 62, to col. 5, line 5); (3) sugar modifications (col. 5, lines 6-22). The terminal modifications alone include a dense list spanning more than an entire column in the printed patent. As such, it can be safely concluded that the skilled person in the art at the time of the present invention was faced with an enormous list of stabilizing chemical modifications but no direction as to which among these could be applied to an siRNA molecule without abrogating activity. None of Monia, Pieken, or Matulic-Adamic provides that direction, which is not surprising because exogenously introduced short interfering RNAs were not known or experimented with until shortly before the publication of Elbashir.

As explained above, Elbashir indeed provided certain limited directions, for example, as to the applicability of 2'-deoxy modifications at the 3'-terminal nucleotides. Meanwhile, Elbashir provided strong evidence that it was ***highly unpredictable*** in the art at the time which of the known stability-enhancing modifications might be applicable to an siRNA, because even with 2'-deoxy modification, when applied more extensively beyond the 3'-terminal nucleotides, which would certainly make the molecule more stable against nucleases, was reported to abrogate RNAi functionality. Another known modification, which was preferred for its ability to enhance stability in antisense molecules, 2'-OMe, was reported by Elbashir to destroy RNAi functionality. Thus, without specific directions as to which of the enormous list of known stability-enhancing chemical modifications to apply, those skilled in the art would need to test each, in every possible pattern, before knowing how RNAi activity might be affected.

The instant claims recite siRNA duplexes that comprise at least two different Northern conformation modifications in a single molecule. With the added limitation of at least five different Northern conformation modifications, the already low predictability between RNAi function and a single modification becomes exponentially lower, which means even more specific directions or suggestions for the claimed invention must be present in the prior art before such claims can be found obvious. But there was simply nothing in the art to suggest picking the claimed modifications, let alone combining them onto a single siRNA molecule without destroying RNAi functionality. The Office's selection of the particular claimed modifications from the many more suitable or even preferred ones listed in the cited references ***can only be*** the result of hindsight in view of what was disclosed and specifically claimed by the instant Applicants. It has long been established that hindsight is an improper basis for an obviousness finding, therefore, the instant claims are not *prima facie* obvious and Applicants respectfully request withdrawal of the rejections.

IV. Conclusions

Therefore, the instant claims are not prima facie obvious and are patentable over the cited prior art references. Applicants therefore respectfully request withdrawal of these rejections.

Respectfully submitted,

Date: October 1, 2009 By: **/Wenfang Chen/**
Wenfang Chen
Reg. No. 52,729
Attorney for Applicants

APPENDIX A

CLAIMS ON APPEAL

1-17. (Canceled)

18. A chemically modified double stranded nucleic acid molecule, wherein:

a) the molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides;

b) each strand is 19 to 29 nucleotides in length;

c) the sense strand, antisense strand, or both strands comprise five or more nucleotides each having a Northern conformation modification; and

d) at least two of said modifications are different from each other.

19. (Canceled)

20. The nucleic acid molecule of claim 18, wherein said nucleic acid molecule comprises one or more ribonucleotides.

21. The nucleic acid molecule of claim 18, wherein said Northern conformation modifications are selected from the group consisting of locked nucleic acid (LNA); 2'-methoxyethoxy; 2'-methyl-thio-ethyl, 2'-deoxy-2'-fluoro, 2'-deoxy-2'-chloro, 2'-azido, 2'-O-trifluoromethyl, 2'-O-ethyl-trifluoromethoxy, 2'-O-difluoromethoxy-ethoxy, 4'-thio and 2'-O-methyl modifications.

22. The nucleic acid molecule of claim 18, wherein the sense strand includes a terminal cap moiety at the 5'-end, the 3'-end, or both of the 5' and 3' ends.

23. The nucleic acid molecule of claim 18, wherein the antisense strand includes a terminal cap moiety at the 3'-end.

24. The nucleic acid molecule of claim 22, wherein said terminal cap moiety comprises an abasic moiety.

25. The nucleic acid molecule of claim 23, wherein said terminal cap moiety comprises an abasic moiety.

26. The nucleic acid molecule of claim 24, wherein said abasic moiety comprises an inverted deoxyabasic moiety.

27. The nucleic acid molecule of claim 25, wherein said abasic moiety comprises an inverted deoxyabasic moiety.

28. The nucleic acid molecule of claim 18, wherein any of the pyrimidine nucleotides in the sense strand are 2'-O-methyl pyrimidine nucleotides.

29. The nucleic acid molecule of claim 18, wherein any of the purine nucleotides in the sense strand are 2'-deoxy purine nucleotides.

30. The nucleic acid molecule of claim 18, wherein any of the pyrimidine nucleotides in the sense strand are 2'-deoxy-2'-fluoro pyrimidine nucleotides.

31. The nucleic acid molecule of claim 18, wherein any of the pyrimidine nucleotides in said antisense strand are 2'-deoxy-2'-fluor pyrimidine nucleotides.

32. The nucleic acid molecule of claim 18, wherein any of the purine nucleotides in said antisense strand are 2'-O-methyl purine nucleotides.

33. A composition comprising the nucleic acid_molecule of claim 18 in a pharmaceutically acceptable carrier or diluent.

APPENDIX B

EVIDENCE APPENDIX

None

APPENDIX C

RELATED PROCEEDINGS APPENDIX

None.

APPENDIX D

AMENDMENTS IN THE CLAIMS

18. (Currently amended) A chemically modified double stranded nucleic acid molecule, wherein:

a) the molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides;

b) each strand is 19 to 29 nucleotides in length;

c) the sense strand, antisense strand, or both strands comprise ~~two~~ <u>five</u> or more nucleotides each having a Northern conformation modification; and

d) at least two of said modifications are different from each other.